

**Synergistic Proteoglycan Compositions for Treatment of Inflammatory Diseases**

The invention is generally related to the treatment of inflammatory conditions.  
5 More specifically, the invention is related to compositions containing inhibitors of mast cell activation and secretion designed to be used as dietary supplement in the treatment of inflammatory conditions.

10 There have been a number of mostly anecdotal reports that the proteoglycan chondroitin sulfate, as well as glucosamine sulfate, a product of the intestinal breakdown of proteoglycans may be helpful in relieving the pain of osteoarthritis: - Shute N. Aching for an arthritis cure. *US News and World Report*, Feb. 10, 1997.- Cowley G. The arthritis cure? *Newsweek*, Feb. 17, 1997.- Foreman J. People, and their pets, tout arthritis remedy. *The Boston Globe*, April 7, 1997; Tye L. Treatment gains scientific attention. *The Boston Globe*, Sep. 25, 2000.

15 A recent meta-analysis showed potential therapeutic benefit of chondroitin sulfate in osteoarthritis [McAlindon *et al. J Am Med Assn.* 283:1469 (2000), and NIH-funded clinical trial OD-98-003 dated 10/10/97]. However, less than 5% of the chondroitin sulfate in available preparations is absorbed orally. Furthermore, such commercial preparations use chondroitin sulfate obtained from cow trachea, with the possible danger of contracting "mad cow disease" [McAlindon *et al.* above]. In fact, the European Union has banned even cosmetics that contain bovine-derived products.

20 Theoharides *et al. British Journal of Pharmacology* 131:1039, (2000) indicated for the first time how proteoglycans such as chondroitin sulfate may work . The paper reported that chondroitin sulfate and, to a lesser degree, glucosamine sulfate, inhibit activation of mast cells that are known to trigger allergy and asthma. Mast cells are also now recognized as important causative intermediary in many



**Copending United States patent application Serial No. 09/056,707, filed 04/08/98, claims the use of proteoglycans, without and with flavonoids, for the treatment of mast cell activation-induced diseases. The information contained therein is incorporated by reference into the present application.**

**An important need therefore exists for dietary formulations suitable for human patients that are synergistic in that they have stronger effects than the sum of the effects of the individual components, and also synergistic with standard clinical treatments of inflammatory conditions, such as osteoarthritis. "Synergistic" is intended to mean: "coordinated or correlated action by two or more structures or drugs" [Stedman's Medical Dictionary, 23rd edition, Williams & Wilkins, Baltimore, 1976]. Such formulations have been discovered, and are described below.**

#### **SUMMARY OF THE INVENTION**

**The invention comprises compositions for human use containing a sulfated proteoglycan and one or more active ingredients selected from the group consisting of a sulfated hexosamine, a flavonoid compound ("flavone"), an organic virgin kernel seed olive oil, S-adenosylmethionine and diphenhydramine, together with appropriate excipients and carriers, said compositions having improved absorptivity from the gastrointestinal tract and anti-inflammatory effects synergistic with each other and synergistic with standard clinical treatment modalities.**

**In one embodiment, the proteoglycan is non-bovine chondroitin sulfate, the sulfated hexosamine is D-glucosamine sulfate, the flavone is quercetin, and the kernel seed olive oil is extra virgin (first pressing, no heat, no refining)).**

**In another embodiment, the compositions are enriched with omega fatty acids and alpha tocopherol.**

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

It has been discovered that a combination of a sulfated proteoglycan, a sulfated D-hexoseamine and a flavone, along with an organic extra virgin kernel seed olive oil, has synergistic anti-inflammatory effects when used as a dietary supplement, without or with a conventional clinical treatment for inflammatory diseases. Such inflammatory diseases result from the activation, degranulation and consequent secretion of inflammatory biochemicals from mast cells, and the resultant inflammatory diseases include the group consisting of: osteoarthritis, cancer, fibromyalgia, inflammatory bowel disease, interstitial cystitis, irritable bowel syndrome, migraines, angina, chronic prostatitis, eczema, arthritis, multiple sclerosis, psoriasis, sun burn, and periodontal disease of the gums.

In a highly preferred embodiment, the sulfated proteoglycan is non-bovine chondroitin sulfate which blocks mast cell activation, degranulation and consequent secretion of inflammatory biochemicals from the mast cells. Other natural sulfated proteoglycans suitable for practicing this invention include keratan sulfate, dermatan sulfate and hyaluronic acid. The preferred biological source of the chondroitin sulfate is shark cartilage which is more-highly sulfated than the standard commercial chondroitin sulfate isolated from cow trachea.

The highly preferred flavone is quercetin which inhibits secretion of inflammatory molecules from mast cells by affecting moesin, a unique 78 kDa mast cell protein [Theoharides *et al.* *J Pharm Exp Therap* 294:810 (2000)]. In addition to quercetin, other flavones suitable in carrying out the invention include myrisetin, genistein and kaempferol.

The olive oil component of the inventive compositions is preferably an organic (no artificial fertilizers, no pesticides, no insecticides) extra virgin (first pressing, no heat, not refined) kernel seed olive oil produced on the island of Crete in Greece. This olive oil increases absorption of the other ingredients of the anti-inflammatory

compositions, and also adds its own content of important anti-oxidants [Bosku, *World Rev Nutr Diet*, 87:56 (2000)], such as omega fatty acids and alpha tocopherol. Although not claimed herein, it has been claimed that kernel seed olive oil has cytoprotective, longevity-producing effects [Trichopoulou *et al. Am J Clin Nutr* 61:1346S (1995); Trichopoulou *et al, Cancer Epid Biomarker Prevention* 9:869 (2000)]. A source of the highly preferred extra virgin kernel seed olive oil is: E.B.E.K., Inc., Commercial, Industrial Enterprises of Crete, 118 Ethnikis Antistasecos, Heraklion, Crete, 71306, Greece.

Supplementation of the compositions described above with the methylation reagent S-adenosylmethionine ("SAM") adds antioxidant, anti-inflammatory and cytoprotective properties, particularly in inflammatory joint diseases. Another supplement to the basic compositions of the invention is diphenhydramine.

The preferred concentration range of the proteoglycan, hexosamine sulfate and flavone components of the oral formulations are 10-3,000 mg per tablet or capsule. The preferred concentration range for S-adenosylmethionine is 3-1,000 mg per capsule or tablet. Generally, where present, the amounts of the olive oil are at least three times those of the other active ingredients. The number of capsules or tablets to be taken per day is determined by the nature and severity of the medical condition, and is readily determinable by the patient's physician. Other representative formulations are described in the examples below.

The compositions of the invention may be formulated in any standard means of introducing pharmaceuticals parenterally into a patient, e.g., by means of tablets or capsules. The compositions of the invention include salves and creams for skin conditions, and mouth washes and toothpaste for periodontal diseases. Standard excipients and carriers for the active ingredients of the inventive compositions are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

Although not bound by any particular mechanism of action of the components of

the claimed compositions, the inventor contemplates that the proteoglycan inhibits the activation and degranulation of the relevant mast cells, while the flavone inhibits the secretion of inflammatory biomolecules from these mast cells. "Activation" and "degranulation" of mast cells are defined herein as is standard and well known in this art.

## EXAMPLES

### Example 1

Table 1 compares chondroitin sulfate-containing commercial products to the present compositions.

Table 1

Comparison of Chondroitin Sulfate-Containing Products to Present Invention		
Product	Most Available Compositions	Present Invention
Main ingredient	Mixture of chondroitin sulfates	Chondroitin sulfate C
Source	Cow trachea	Shark cartilage
Amount per capsule or tablet	150 mg	10-3000 mg
Degree of sulfation	Low	High
Absorption from g.i. tract	<5%	>15%
Target	Unknown	Mast cells, bone cells
Other ingredients	Vitamins, fish oils (some preparations)	Flavones, omega-fatty acids, alpha-tocopherol, kernel olive seed oil, SAM

<b>Advantages</b>	<b>None known</b>	<b>Anti-allergic, anti-inflammatory, anti-oxidant, cytoprotective</b>
<b>Adverse effects</b>	<b>Risk of mad cow disease, stomach upset, allergy to fish products</b>	<b>None known</b>
<b>Relevant conditions</b>	<b>Osteoarthritis</b>	<b>Angina, arthritis, chronic prostatitis, eczema, fibromyalgia, interstitial cystitis, irritable bowel syndrome, inflammatory bowel disease, migraines multiple sclerosis, psoriasis, periodontal disease.</b>
<b>Scientific publications</b>	<b>None found</b>	<b>Theoharides et al. <i>Br J Pharm</i> 131:1039 ( 2000) Middleton et al. <i>Pharm Rev</i> 52:673 ( 2000)</b>

## Example 2

### Composition of Formulation One (ALGONOT-PLUS, registered mark)

#### Dietary Supplement

Two capsules to be taken twice daily, at least one hour before meals

#### Active ingredients:

* Chondroitin sulfate	300 mg
* D-Glucosamine sulfate	300 mg
* Quercetin	300 mg
* extra virgin kernel seed olive oil	900 mg

Hypo-allergenic, free from: artificial colors or flavors, corn, milk products, preservatives, salt, starch, sugar, wheat or yeast.

## Example 3

### Composition of Formulation Two (ALGONOT-PREVENT, registered mark)

#### Dietary Supplement

Two capsules to be taken twice daily, one hour before meals

#### Active Ingredients

* Chondroitin sulfate	300 mg
* Glucosamine sulfate	300 mg
* Quercetin	300 mg
* S-adenosylmethionine	100 mg
* extra virgin kernel seed olive oil	900 mg



**Hypo-allergenic. Free from: artificial colors or flavors, corn, milk products, preservatives, salt, starch, sugar, wheat or yeast.**

#### **Example 4**

##### **Composition of Formulation Three (ALGONOT-PROTECT, reg. mark)**

**Skin ointment or cream. Apply three times per day to affected areas.**

<b><u>Active Ingredient</u></b>	<b><u>% by weight</u></b>
<b>*Chondroitin sulfate</b>	<b>5</b>
<b>*Quercetin</b>	<b>3</b>
<b>*Extra virgin kernel seed olive oil</b>	<b>15</b>

#### **Example 5**

##### **Composition of Formulation Four (ALGONOT-ALLERGY, reg. mark)**

**\*Formulation Three plus diphenhydramine, 5 % by weight.**

#### **Example 6**

##### **Composition of Formulation Five (ALGONOT-PERIO)**

##### **Mouth wash**

**\*Chondroitin sulfate, 0.4 M**

**\*Optionally: D-glucosamine sulfate, 0.4M; quercetin, 0.3M; SAM 0.15M**

**\*In a standard mouth wash vehicle.**

### Example 7

#### Composition of Formulation Six (ALGONOT-DENTAL)

5	<b>Tooth paste</b>	<b>mg%</b>
	<b>*Chondroitin sulfate</b>	<b>5</b>
	<b>*Quercetin</b>	<b>3</b>
	<b>*In a standard tooth paste vehicle</b>	

### Example 8

#### Composition of Formulation Seven (ALGONOT-SUNSCREEN)

15	<b>Active ingredients</b>	<b>mg%</b>
	<b>*Chondroitin sulfate</b>	<b>5</b>
	<b>*Quercetin</b>	<b>3</b>
	<b>*Sun screen (e.g., TiO<sub>2</sub>)</b>	<b>5</b>

**I claim:**

**1. A dietary composition with synergistic anti-inflammatory properties in conditions induced by the activation of mast cell secretion and consequent degranulation of said cells and release of inflammatory biomolecules from said cells, comprising a proteoglycan sulfate, and, optionally, one or more of a hexosamine sulfate, a flavone, an organic extra virgin kernel seed olive oil, S-adenosylmethionine and diphenhydramine, in an appropriate excipient or vehicle.**

**2. The composition according to claim 1, wherein said sulfated proteoglycan is selected from the group consisting of non-bovine chondroitin sulfate, keratan sulfate, dermatan sulfate and hyaluronic acid.**

**3. The composition according to claim 2, wherein said chondroitin sulfate is chondroitin sulfate C derived from shark cartilage.**

**4. The composition according to claim 1, wherein said hexosamine sulfate is D-glucosamine sulfate.**

**5. The composition according to claim 1, wherein said flavone is selected from the group consisting of quercetin, myricetin, genistein and kaempferol.**

**6. The composition according to claim 1, wherein said olive oil contains omega fatty acids and alpha-tocopherol.**

**7. A composition for treating inflammatory diseases according to claim 1, said composition being for parenteral use, comprising 300 mg each of non-bovine chondroitin sulfate C, quercetin and D-glucosamine sulfate, with an organic extra virgin kernel seed olive oil containing omega fatty acids and alpha tocopherol.**

**8. The composition according to claim 7, further supplemented with 100 mg of S-**

**adenosylmethionine.**

**9. A composition for treating inflammatory diseases according to claim 1, said composition consisting of an ointment or cream for topical application, comprising, in mg % , chondroitin sulfate, 5; and, optionally, one or more of D-glucosamine sulfate, 5; quercetin, 3; and, extra virgin kernel seed olive oil,15.**

**10. A composition according to claim 9, supplemented by diphenhydramine, 5mg%.**

**11. A composition for treating inflammatory diseases according to claim 1, said composition consisting of a mouth wash composition, comprising chondroitin sulfate, 0.4M, and, optionally, one or more of D-glucosamine sulfate, 0.4M, quercetin, 0.3M, and S-adenosylmethionine, 0.15M, in a mouth wash vehicle.**

**12. A composition for treating inflammatory diseases according to claim 1, said composition consisting of a tooth paste, comprising, in mg%, chondroitin sulfate, 5; and one or more of D-glucosamine sulfate, 5; and quercetin, 3, in a tooth paste vehicle.**

**13. A composition for treating inflammatory diseases according to claim 1, said composition consisting of a sunscreen composition, comprising ,in mg% , chondroitin sulfate, 5; and, optionally, one or more of D-glucosamine sulfate, 5; quercetin, 3; and titanium dioxide, 5; in a sun screen vehicle.**

**15. ALGONOT-PLUS**

**16. ALGONOT- PREVENT**

**17. ALGONOT-PROTECT**

**18. ALGONOT-ALLERGY**

**19. ALGONOT-PERIO**

**20. ALGONOT-DENTAL**

**21. ALGONOT-SUNSCREEN**

**22. A method of treating a subject suffering from an inflammatory disease resulting from activation and degranulation of mast cells and secretion of inflammatory molecules from said cells, said inflammatory diseases selected from the group consisting of osteoarthritis, cancer, fibromyalgia, inflammatory bowel disease, interstitial cystitis, irritable bowel syndrome , migraines, angina, chronic prostatitis, eczema, arthritis, multiple sclerosis, psoriasis, sun burn, and periodontal disease, comprising the step of administering to said subject an effective amount of a composition according to claim 1.**

## ABSTRACT

**Compositions with synergistic anti-inflammatory effect in inflammatory diseases resulting from activation and consequent degranulation of mast cell and followed by secretion of inflammatory biomolecules from the activated mast cells, composed of a heavily sulfated, non-bovine proteoglycan such as chondroitin sulfate C and one or more of a hexosamine sulfate such as D-glucosamine sulfate, a flavone such as quercetin, a special organic extra virgin kernel seed olive oil, S-adenosylmethionine and diphenhydramine.**

**Synergistic Dietary Compositions for Treatment of Inflammatory Diseases**

The invention is generally related to the treatment of inflammatory conditions.  
5 More specifically, the invention is related to compositions containing inhibitors of mast cell activation and secretion designed to be used as dietary supplement in the treatment of inflammatory conditions.

There have been a number of mostly anecdotal reports that the proteoglycan  
10 chondroitin sulfate, as well as glucosamine sulfate, a product of the intestinal breakdown of proteoglycans may be helpful in relieving the pain of osteoarthritis: -  
Shute N. Aching for an arthritis cure. *US News and World Report*, Feb. 10, 1997.-  
Cowley G. The arthritis cure? *Newsweek*, Feb. 17, 1997.- Foreman J. People, and their  
15 pets, tout arthritis remedy. *The Boston Globe*, April 7, 1997; Tye L. Treatment gains scientific attention. *The Boston Globe*, Sep. 25, 2000.

A recent meta-analysis showed potential therapeutic benefit of chondroitin  
sulfate in osteoarthritis [McAlindon *et al. J Am Med Assn.* 283:1469 (2000), and NIH-  
funded clinical trial OD-98-003 dated 10/10/97]. However, less than 5% of the  
20 chondroitin sulfate in available preparations is absorbed orally. Furthermore, such commercial preparations use chondroitin sulfate obtained from cow trachea, with the possible danger of contracting "mad cow disease" [McAlindon *et al.* above]. In fact, the European Union has banned even cosmetics that contain bovine-derived products.

25 Theoharides *et al. British Journal of Pharmacology* 131:1039, (2000) indicated for the first time how proteoglycans such as chondroitin sulfate may work . The paper reported that chondroitin sulfate and, to a lesser degree, glucosamine sulfate, inhibit activation of mast cells that are known to trigger allergy and asthma. Mast cells are also now recognized as important causative intermediary in many





**Copending United States patent application Serial No. 09/056,707, filed 04/08/98, claims the use of proteoglycans, without and with flavonoids, for the treatment of mast cell activation-induced diseases. The information contained therein is incorporated by reference into the present application.**

**An important need therefore exists for dietary formulations suitable for human patients that are synergistic in that they have stronger effects than the sum of the effects of the individual components, and also synergistic with standard clinical treatments of inflammatory conditions, such as osteoarthritis. "Synergistic" is intended to mean: "coordinated or correlated action by two or more structures or drugs" [Stedman's Medical Dictionary, 23rd edition, Williams & Wilkins, Baltimore, 1976]. Such formulations have been discovered, and are described below.**

#### **SUMMARY OF THE INVENTION**

**The invention comprises compositions for human use containing a sulfated proteoglycan and one or more active ingredients selected from the group consisting of a sulfated hexosamine, a flavonoid compound ("flavone"), an organic virgin kernel seed olive oil, S-adenosylmethionine and diphenhydramine, together with appropriate excipients and carriers, said compositions having improved absorptivity from the gastrointestinal tract and anti-inflammatory effects synergistic with each other and synergistic with standard clinical treatment modalities.**

**In one embodiment, the proteoglycan is non-bovine chondroitin sulfate, the sulfated hexosamine is D-glucosamine sulfate, the flavone is quercetin, and the kernel seed olive oil is extra virgin (first pressing, no heat, no refining)).**

**In another embodiment, the compositions are enriched with omega fatty acids and alpha tocopherol.**

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

It has been discovered that a combination of a sulfated proteoglycan, a sulfated D-hexoseamine and a flavone, along with an organic extra virgin kernel seed olive oil, has synergistic anti-inflammatory effects when used as a dietary supplement, without or with a conventional clinical treatment for inflammatory diseases. Such inflammatory diseases result from the activation, degranulation and consequent secretion of inflammatory biochemicals from mast cells, and the resultant inflammatory diseases include the group consisting of: osteoarthritis, cancer, fibromyalgia, inflammatory bowel disease, interstitial cystitis, irritable bowel syndrome, migraines, angina, chronic prostatitis, eczema, arthritis, multiple sclerosis, psoriasis, sun burn, and periodontal disease of the gums.

In a highly preferred embodiment, the sulfated proteoglycan is non-bovine chondroitin sulfate which blocks mast cell activation, degranulation and consequent secretion of inflammatory biochemicals from the mast cells. Other natural sulfated proteoglycans suitable for practicing this invention include keratan sulfate, dermatan sulfate and hyaluronic acid. The preferred biological source of the chondroitin sulfate is shark cartilage which is more-highly sulfated than the standard commercial chondroitin sulfate isolated from cow trachea.

The highly preferred flavone is quercetin which inhibits secretion of inflammatory molecules from mast cells by affecting moesin, a unique 78 kDa mast cell protein [Theoharides *et al.* *J Pharm Exp Therap* 294:810 (2000)]. In addition to quercetin, other flavones suitable in carrying out the invention include myrisetin, genistein and kaempferol.

The olive oil component of the inventive compositions is preferably an organic (no artificial fertilizers, no pesticides, no insecticides) extra virgin (first pressing, no heat, not refined) kernel seed olive oil produced on the island of Crete in Greece. This olive oil increases absorption of the other ingredients of the anti-inflammatory

compositions, and also adds its own content of important anti-oxidants [Bosku, *World Rev Nutr Diet*, 87:56 (2000)], such as omega fatty acids and alpha tocopherol. Although not claimed herein, it has been claimed that kernel seed olive oil has cytoprotective, longevity-producing effects [Trichopoulou *et al. Am J Clin Nutr* 61:1346S (1995); Trichopoulou *et al, Cancer Epid Biomarker Prevention* 9:869 (2000)]. A source of the highly preferred extra virgin kernel seed olive oil is: E.B.E.K., Inc., Commercial, Industrial Enterprises of Crete, 118 Ethnikis Antistasecos, Heraklion, Crete, 71306, Greece.

Supplementation of the compositions described above with the methylation reagent S-adenosylmethionine ("SAM") adds antioxidant, anti-inflammatory and cytoprotective properties, particularly in inflammatory joint diseases. Another supplement to the basic compositions of the invention is diphenhydramine.

The preferred concentration range of the proteoglycan, hexosamine sulfate and flavone components of the oral formulations are 10-3,000 mg per tablet or capsule. The preferred concentration range for S-adenosylmethionine is 3-1,000 mg per capsule or tablet. Generally, where present, the amounts of the olive oil are at least three times those of the other active ingredients. The number of capsules or tablets to be taken per day is determined by the nature and severity of the medical condition, and is readily determinable by the patient's physician. Other representative formulations are described in the examples below.

The compositions of the invention may be formulated in any standard means of introducing pharmaceuticals parenterally into a patient, e.g., by means of tablets or capsules. The compositions of the invention include salves and creams for skin conditions, and mouth washes and toothpaste for periodontal diseases. Standard excipients and carriers for the active ingredients of the inventive compositions are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

Although not bound by any particular mechanism of action of the components of

the claimed compositions, the inventor contemplates that the proteoglycan inhibits the activation and degranulation of the relevant mast cells, while the flavone inhibits the secretion of inflammatory biomolecules from these mast cells. “Activation” and “degranulation” of mast cells are defined herein as is standard and well known in this art.

EXAMPLES

Example 1

Table 1 compares chondroitin sulfate-containing commercial products to the present compositions.

Table 1

Comparison of Chondroitin Sulfate-Containing Products to Present Invention		
Product	Most Available Compositions	Present Invention
Main ingredient	Mixture of chondroitin sulfates	Chondroitin sulfate C
Source	Cow trachea	Shark cartilage
Amount per capsule or tablet	150 mg	10-3000 mg
Degree of sulfation	Low	High
Absorption from g.i. tract	<5%	>15%
Target	Unknown	Mast cells, bone cells
Other ingredients	Vitamins, fish oils (some preparations)	Flavones, omega-fatty acids, alpha-tocopherol, kernel olive seed oil, SAM

<b>Advantages</b>	<b>None known</b>	<b>Anti-allergic, anti-inflammatory, anti-oxidant, cytoprotective</b>
<b>Adverse effects</b>	<b>Risk of mad cow disease, stomach upset, allergy to fish products</b>	<b>None known</b>
<b>Relevant conditions</b>	<b>Osteoarthritis</b>	<b>Angina, arthritis, chronic prostatitis, eczema, fibromyalgia, interstitial cystitis, irritable bowel syndrome, inflammatory bowel disease, migraines multiple sclerosis, psoriasis, periodontal disease.</b>
<b>Scientific publications</b>	<b>None found</b>	<b>Theoharides et al. <i>Br J Pharm</i> 131:1039 ( 2000) Middleton et al. <i>Pharm Rev</i> 52:673 ( 2000)</b>

## Example 2

### Composition of Formulation One (ALGONOT-PLUS, registered mark)

#### Dietary Supplement

Two capsules to be taken twice daily, at least one hour before meals

#### Active ingredients:

* Chondroitin sulfate	300 mg
* D-Glucosamine sulfate	300 mg
* Quercetin	300 mg
* extra virgin kernel seed olive oil	900 mg

Hypo-allergenic, free from: artificial colors or flavors, corn, milk products, preservatives, salt, starch, sugar, wheat or yeast.

## Example 3

### Composition of Formulation Two (ALGONOT-PREVENT, registered mark)

#### Dietary Supplement

Two capsules to be taken twice daily, one hour before meals

#### Active Ingredients

* Chondroitin sulfate	300 mg
* Glucosamine sulfate	300 mg
* Quercetin	300 mg
* S-adenosylmethionine	100 mg
* extra virgin kernel seed olive oil	900 mg

**Hypo-allergenic. Free from: artificial colors or flavors, corn, milk products, preservatives, salt, starch, sugar, wheat or yeast.**

#### **Example 4**

##### **Composition of Formulation Three (ALGONOT-PROTECT, reg. mark)**

**Skin ointment or cream. Apply three times per day to affected areas.**

<b><u>Active Ingredient</u></b>	<b><u>% by weight</u></b>
<b>*Chondroitin sulfate</b>	<b>5</b>
<b>*Quercetin</b>	<b>3</b>
<b>*Extra virgin kernel seed olive oil</b>	<b>15</b>

#### **Example 5**

##### **Composition of Formulation Four (ALGONOT-ALLERGY, reg. mark)**

**\*Formulation Three plus diphenhydramine, 5 % by weight.**

#### **Example 6**

##### **Composition of Formulation Five (ALGONOT-PERIO)**

##### **Mouth wash**

**\*Chondroitin sulfate, 0.4 M**

**\*Optionally: D-glucosamine sulfate, 0.4M; quercetin, 0.3M; SAM 0.15M**

**\*In a standard mouth wash vehicle.**

### Example 7

#### Composition of Formulation Six (ALGONOT-DENTAL)

5	<u>Tooth paste</u>	<u>mg%</u>
	*Chondroitin sulfate	5
	*Quercetin	3
	*In a standard tooth paste vehicle	

### Example 8

#### Composition of Formulation Seven (ALGONOT-SUNSCREEN)

	<u>Active ingredients</u>	<u>mg%</u>
15	*Chondroitin sulfate	5
	*Quercetin	3
	*Sun screen (e.g., TiO <sub>2</sub> )	5